Mini Review Article

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Preclinical Stroke Exploration and Translational Disappointment

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Abstract

Translation from preclinical research has always been a topic of debate, despite the remarkable progress made in comprehending the cellular, molecular, and pathophysiological aspects of stroke. Even though thousands of experimental compounds have been shown to protect the brain, they have failed in clinical trials, leaving researchers and stakeholders in limbo. However the disappointments portrayed have been horrifying, they likewise allow us an opportunity to pull together on the inadequacies. For better translational worth, and confirmations from preclinical investigations ought to be powerful and solid. The design of a preclinical study has many variables that affect the results. As a result, this review focuses on the aspects that need to be taken into consideration for a well planned preclinical study while adhering to guidelines. These aspects include the study design, commonly used animal models, their limitations, and the concept of metacentric preclinical randomized controlled trials. It also pays special attention to a variety of preventable attritions, such as comorbidities, aged animals, and the time of administration, outcome measures, and physiological variables. In order to produce a neuroprotectant with greater translational value from a well-defined preclinical study, we present an overview of a wide range of practical aspects that could be implemented.

Keywords: Ischemic Stroke • Translational Failure • Preclinical Study Design • Animal Models • Preclinical Randomized Controlled Trials

Introduction

The second most common cause of death and the leading cause of morbidity worldwide is stroke, a cerebrovascular disorder. According to one study, there were approximately 11.9 million incident cases, 104.1 million prevalent cases, and 6.6 million deaths worldwide in 2017. Stroke forces an enormous financial weight, as the survivors of intense stroke remain actually or intellectually disadrained and reliant upon their families. Due to the fact that many stroke related deaths are not reported, the data may be higher [1].

Preclinical research has made great progress in understanding the pathophysiology of stroke over the past three decades, but the only treatment options are revascularization with mechanical thrombectomy or recombinant tissue plasminogen activator (rtPA). The use of rtPA has been restricted to 2–4% of patients due to the risk of bleeding and its short therapeutic window, whereas mechanical thrombectomy is only used for occlusions of larger vessels. Neuro protection, which rescues the potentially salvageable tissue by modulating various cell survival or death pathways, is another very important therapeutic approach in addition to revascularization. However, almost all neuro protectants have failed in clinical trials despite promising results in animal models. More than 200 drugs and combinations have been tested in approximately 150 clinical trials, with over a thousand experimental drugs demonstrating neuro protection in various animal models. However, the majority of them were unsuccessful due to either lack of efficacy or an increase in damage, resulting in significant financial loss but no therapeutic benefit [2-3].

Discussion

Selection of model animal

The translational success of therapeutic agents in clinical settings is significantly influenced

by the choice of an appropriate animal model for preclinical studies. Because ischemic stroke is a highly complex pathophysiological entity, no single model can accurately simulate the various clinical variables. As a result, when choosing an animal model, it is essential to define specific questions that guarantee the specificity of the model and the species used. In the majority of stroke research, smaller animals like mice and rats are preferred due to their lower cost, ease of handling, and greater acceptability. Although rats are frequently used as rodents, mice with the ability to be genetically modified are preferable for studying the disease's mechanistic aspects. Due to the fact that occlusion of the Middle Cerebral Artery (MCA) is responsible for 70% of all clinically observed ischemic infarcts, there are numerous and, in some cases, very distinct animal models for simulating ischemic stroke that targets MCA. A few fundamental and most commonly used MCA occlusion models, such as the thromboembolic model, intraluminal suture insertion, and endothelia injection, can ultimately be reduced from the plethora. The majority of preclinical studies in recent decades have utilized rodents. Even though these have been very helpful in figuring out the disease's pathophysiology, their constant failure at the clinical level has made people wonder if rodents are good animals. The translational failure may be explained by interesting differences between rodents and humans. Compared to humans, rats have a significantly different immune response to injury caused by a stroke [4].

The natural stroke that occurs in dogs has recently received a lot of attention. Clinical signs of a sudden stroke in dogs are similar to those in humans, including visual disturbances, contralateral motor dysfunction, and facial paralysis. In addition, they are superior to other artificially induced ischemia models due to their low cost, natural occurrence, access to high quality medical care, similar anatomical characteristics, such as a gyrencephalic brain with the same site of occlusion, and similar comorbid conditions [5].

Utilization of Young and Old Animals in Sequence

Age is associated with an increased risk of stroke clinically; According to previous study over 85 year olds account for 30% of strokes and 50% of all strokes. Due to accumulated risk factors like smoking, alcohol consumption, hypertension, diabetes, and atrial fibrillation, the elderly population is more likely to suffer a stroke. Additionally, the prevalence of stroke in young adults is epidemically rising due to shifting lifestyles and socioeconomic status. In spite of the fact that, the gamble is expanding in youthful grown ups, the older still structure most of stroke populace with higher mortality what's more, extremely poor useful results. In addition to having an impact on the pharmacokinetics and pharmacodynamics of interventional drug agents, aging also slows down the process of spontaneous recovery due to increased microglial proliferation, decreased cortical neurogenesis, an increased risk of converting salvageable penumbra into infarct core, and an increased risk of hemorrhage following thrombolytic therapy . Older animals may have less edema than younger animals due to the absence of sodium potassium chloride co transporter expression. Interestingly, recent research found that older animals were more likely to have neutrophil pathogenicity, indicating that targeted therapies targeting neutrophils are more effective in older animals than in younger ones. Thus, the results acquired in youthful creatures are simply deciphered on matured stroke patients partaking in clinical preliminaries [6].

Time of dosage

Preclinical studies typically initiate treatment either before or within the first one to two hours following a stroke in order to provide best opportunity for determining efficacy. According to a meta analysis that was recently published, drug administration times were within the first three hours in 82.3 percent of preclinical studies and more than six hours in clinical trials. Establishing a possible therapeutic time window is crucial to limiting translational failure in clinical settings, even though early administration of therapeutic agents in animal studies is a good first step in identifying promising agents [7-9].

Outcomes of the study

Because it is noninvasive, magnetic resonance imaging (Diffussion, perfusion, and T2 weighted images) can be used for a variety of tasks, including high resolution anatomical detailed analysis, multi

parametric physiological mapping, and model validation, determining the evolution of an ischemic lesion, and determining the effect of a therapeutic intervention. In order to estimate brain damage, MR imaging should be used instead of TTC, H&E, or CV staining. Perfusion and dissemination weighted imaging crisscross gives a great gauge of the obscuration making direct evaluation of salvageable tissue recuperation in sub persistent time windows conceivable. Additionally, fMRI enables evaluation of the modulation of the physiological reorganization by interventions. In a nutshell, a collection of the most pertinent tests can be used to examine functional responses, such as the Rota Rod Sensory Motor Test, Grip Strength Test, Adhesive tape removal test, cylinder test, Morris water maze cognitive impairment test, and neurological deficit tests using Forelimb Flexion, Resistance to Lateral Push, circling, and non-spontaneous movement . Additionally, the modified neurological severity score, a more in depth scoring system that incorporates motor, sensory, reflex, and balance assessments and ranges from 3 to 18 points, has been utilized and recommended [10].

Conclusion

The heterogeneous nature of stroke has, without a doubt, made finding treatment extremely difficult. The essential variables needed to enhance stroke preclinical research were discussed in this review. In addition, it is important to note that it may not be sufficient to concentrate on and improve preclinical studies alone; instead, it is equally important to carefully apply this knowledge when designing clinical trials. To close the translational gap, selecting a predictive and validated animal model is crucial. The most widely used and well accepted ischemic stroke models that target MCA have greatly contributed to our comprehension of its fundamental concepts. It is highly improbable that a novel neuro protective will work in large, expensive clinical trials without rigorous, robust, and detailed preclinical testing. In order to test the compound in conditions similar to those found in clinical settings, it is necessary to place particular emphasis on the design of a robust and well planned preclinical study, the collection and reporting of all data, including negative results, the sequential use of young to old animals in multiple models, the use of animals with comorbidities, the exploration of the time of dosing, the monitoring of physiological parameters, and outcome measures. The current translational problem will undoubtedly be solved by strictly adhering to the guidelines and multi centric preclinical studies that are available. Even though these can substantially increase the time and money spent on experiments, finding just one drug with the potential to be clinically effective would more than pay for the time and money spent on them and restore the trust of the stroke research community.

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